

MEANS AND METHOD FOR A QUADRUPOLE SURFACE INDUCED
DISSOCIATION QUADRUPOLE TIME-OF-FLIGHT MASS SPECTROMETER

1 TECHNICAL FIELD OF THE INVENTION

2 The present invention relates generally to means and method
3 whereby ions from an ion source are selectively transmitted
4 through a multipole apparatus having the capability of producing
5 ion fragments via collisions with a surface or a gas to be
6 readily analyzed by a TOF mass spectrometer. More specifically,
7 a method and apparatus are described which use a plurality
8 (preferably three) of multipole devices, a collision surface
9 (for SID), and/or a collision gas (for CID) to produce fragment
10 ions of a selected m/z range for subsequent mass analysis.

11
12 BACKGROUND OF THE PRESENT INVENTION

13 The present invention relates to a multipole ion system with
14 a collision surface for use in TOF mass spectrometry. The
15 methods for transmitting ions and producing ion fragments
16 described herein are enhancements of the techniques that are
17 referred to in the literature relating to mass spectrometry.

18 Mass spectrometry is an important tool in the analysis of a
19 wide range of chemical compounds. Specifically, mass

1 spectrometers can be used to determine the molecular weight of
2 sample compounds. The analysis of samples by mass spectrometry
3 consists of three main steps - formation of gas phase ions from
4 sample material, mass analysis of the ions to separate the ions
5 from one another according to ion mass, and detection of the
6 ions. A variety of means exist in the field of mass spectrometry
7 to perform each of these three functions. The particular
8 combination of means used in a given spectrometer determine the
9 characteristics of that spectrometer.

10 To mass analyze ions, for example, one might use a magnetic
11 (B) or electrostatic (E) analyzer. Ions passing through a
12 magnetic or electrostatic field will follow a curved path. In a
13 magnetic field the curvature of the path will be indicative of
14 the momentum-to-charge ratio of the ion. In an electrostatic
15 field, the curvature of the path will be indicative of the
16 energy-to-charge ratio of the ion. If magnetic and electrostatic
17 analyzers are used consecutively, then both the momentum-to-
18 charge and energy-to-charge ratios of the ions will be known and
19 the mass of the ion will thereby be determined. Other mass
20 analyzers are the quadrupole (Q), the ion cyclotron resonance
21 (ICR), the time-of-flight (TOF), and the quadrupole ion trap

1 analyzers.

2 Before mass analysis can begin, however, gas phase ions must
3 be formed from sample material. If the sample material is
4 sufficiently volatile, ions may be formed by electron impact (EI)
5 or chemical ionization (CI) of the gas phase sample molecules.
6 For solid samples (e.g. semiconductors, or crystallized
7 materials), ions can be formed by desorption and ionization of
8 sample molecules by bombardment with high energy particles.
9 Secondary ion mass spectrometry (SIMS), for example, uses keV
10 ions to desorb and ionize sample material. In the SIMS process a
11 large amount of energy is deposited in the analyte molecules. As
12 a result, fragile molecules will be fragmented. This
13 fragmentation is undesirable in that information regarding the
14 original composition of the sample -- e.g., the molecular weight
15 of sample molecules -- will be lost.

16 For more labile, fragile molecules, other ionization methods
17 now exist. The plasma desorption (PD) technique was introduced
18 by Macfarlane et al. in 1974 (Macfarlane, R. D.; Skowronski, R.
19 P.; Torgerson, D. F., *Biochem. Biophys. Res Commun.* 60 (1974)
20 616). Macfarlane et al. discovered that the impact of high
21 energy (MeV) ions on a surface, like SIMS would cause desorption

1 and ionization of small analyte molecules, however, unlike SIMS,
2 the PD process results also in the desorption of larger, more
3 labile species -- e.g., insulin and other protein molecules.

4 Lasers have been used in a similar manner to induce
5 desorption of biological or other labile molecules. See, for
6 example, VanBreeman, R.B.; Snow, M.; Cotter, R.J., *Int. J. Mass*
7 *Spectrom. Ion Phys.* **49** (1983) 35; Tabet, J.C.; Cotter, R.J.,
8 *Anal. Chem.* **56** (1984) 1662; or Olthoff, J.K.; Lys, I.; Demirev,
9 P.; Cotter, R. J., *Anal. Instrument.* **16** (1987) 93. Cotter et
10 al. modified a CVC 2000 time-of-flight mass spectrometer for
11 infrared laser desorption of involatile biomolecules, using a
12 Tachisto (Needham, Mass.) model 215G pulsed carbon dioxide laser.
13 The plasma or laser desorption and ionization of labile molecules
14 relies on the deposition of little or no energy in the analyte
15 molecules of interest. The use of lasers to desorb and ionize
16 labile molecules intact was enhanced by the introduction of
17 matrix assisted laser desorption ionization (MALDI) (Tanaka, K.;
18 Waki, H.; Ido, Y.; Akita, S.; Yoshida, Y.; Yoshica, T., *Rapid*
19 *Commun. Mass Spectrom.* **2** (1988) 151 and Karas, M.; Hillenkamp,
20 F., *Anal. Chem.* **60** (1988) 2299). In the MALDI process, an analyte
21 is dissolved in a solid, organic matrix. Laser light of a

1 wavelength that is absorbed by the solid matrix but not by the
2 analyte is used to excite the sample. Thus, the matrix is
3 excited directly by the laser, and the excited matrix sublimes
4 into the gas phase carrying with it the analyte molecules. The
5 analyte molecules are then ionized by proton, electron, or cation
6 transfer from the matrix molecules to the analyte molecules.
7 This process, MALDI, is typically used in conjunction with time-
8 of-flight mass spectrometry (TOFMS) and can be used to measure
9 the molecular weights of proteins in excess of 100,000 daltons.

10 Time-of-flight mass spectrometry (or TOFMS) plays an
11 important role in the analysis of chemical compounds.
12 Specifically, TOF mass spectrometers are useful in determining
13 the molecular weight of sample compounds. In orthogonal TOF mass
14 spectrometers ions pass from the source into the analyzer in a
15 direction which is orthogonal to the axis of the analyzer. The
16 concept of orthogonal acceleration using TOFMS was disclosed by
17 O'Hallran et al. in 1964 (G.J. O'Halloran et al., *Determination*
18 *of Chemical Species Prevalent in a Plasma Jet*. Technical
19 Documentary Report No. ASD-TDR-62-664, prepared under contract AF
20 33(616)-8374 by the Bendix Corp. Research Laboratories (1964)).
21 O'Hallran et al. also introduced the application of TOF mass

1 analysis to ionization sources at elevated pressure. One
2 advantage to using orthogonal acceleration and elevated pressure
3 ionization sources is that ions form a continuous beam and can be
4 mass analyzed more efficiently. Also, with the "orthogonal
5 acceleration" method, the mass analysis occurs along an axis
6 which is orthogonal to the ion's initial direction of motion. As
7 a result, the initial energy of the ions does not significantly
degrade the mass resolution of the instrument.

Chien and Lubman demonstrated the advantage of using a
quadrupole ion trap - TOF mass analyzer in the analysis of
electrospray produced ions (Chien, B.M.; Lubman, D.M., *Anal.*
Chem. **66**, 1630(1994)). The ions from the electrospray source are
transferred with a high efficiency to the TOF analyzer and ions
may be preselected and collision induced dissociation on these
ions may be performed. One disadvantage with this method is low
mass resolving power. Also, there are restrictions in the time
required for cooling the ions and cycling the pressure in the ion
trap.

Chernushevich et al discloses the use of ion introduction
into an RF-quadrupole ion guide at a high gas pressure (I.V.
Chernushevich, Proceedings of the 44th ASMS Conference of Mass

1 Spectrometry and Allied Topics, May 12-16, 1173 (1996)).
2 Similarly, Douglas discloses ion introduction into a quadrupole
3 ion trap rather than a TOF analyzer (D.J. Douglas, USPN
4 5,179,278). Here, the ions are cooled by passage through the
5 quadrupole at elevated pressure and are then transferred into a
6 low pressure region containing a quadrupole trap analyzer. This
7 "collisional focusing" method has also been incorporated with the
8 "orthogonal acceleration" method in TOF mass spectrometry to
9 obtain a higher resolution mass spectrum.

10 Morris et al. discloses the use of additional multipole
11 devices to preselect ions and induce collision dissociation in
12 the trap - TOF analyzer (H.R. Morris et al., *Rapid Comm. Mass*
13 *Spectrom.* 10, 889(1996)). Their first multipole device is used
14 to cool ions then a second multipole is used for mass selection,
15 and a third multipole is used for collision induced dissociation.
16 Collision induced dissociation experiments were also disclosed in
17 Lubman (B.M. Chien, S.M. Michael, D.M. Lubman, *Int J. Mass*
18 *Spectrom. Ion Process.*, 131, 149 (1994), B.M. Chien, D.M. Lubman,
19 *Anal. Chem.* 66, 1630 (1994)).

20 Ions extracted from a multipole device and orthogonally
21 accelerated in the direction of the axis of the analyzer will

1 have a significant kinetic energy orthogonal to the axis of the
2 analyzer. This initial kinetic energy will cause the ions to
3 drift perpendicularly to the analyzer axis. This kinetic energy
4 must be accounted for in order to prevent ion loss and to ensure
5 ion detection. M.A. Park discloses a multideflector for
6 correcting for such kinetic energies by deflecting the ion beam
7 on the analyzer axis (US patents 5,696,375 and 6,107,625).

8
9
10 Also, during the extracting process, the kinetic energy
11 component of ions in the direction along the axis of the TOF
12 analyzer - and therefore orthogonal to the axis of the multipole
13 ion guide - will have a strong influence on the resolution that
14 can be achieved by a TOF analyzer. To achieve best results, ions
15 should be have near thermal kinetic energies - achieved by
16 cooling in the ion guide.

17 High efficiency in transmitting ions from a multipole to a
18 TOF analyzer requires that the spatial extent of the ion beam
19 perpendicular to the axis of the analyzer be large compared to,
20 for example, that of prior art MALDI-TOF designs. As a result,
21 some prior art devices (i.e. the two stage reflectron taught by
R. Frye in USPN 4,731,532) cannot be used with the orthogonal
multipole orthogonal TOF instruments described above.

1 An alternative "method and device for orthogonal ion
2 injection into a time-of-flight mass spectrometer", proposed in
3 Franzen United States Pat. No. 5,763,878 (the "'878 patent").
4 According to the '878 patent, ions are ejected from a multipole
5 ion guide of design similar to that of Chernushevich *et al.* into
6 a time-of-flight analyzer and in a direction orthogonal to the
7 axis of the multipole device. In trapping mode an RF potential
8 is applied to the poles of the multipole device whereas in
9 ejection mode, DC potentials are applied to the poles of the
10 multipole device so as to accelerate the ions in a direction
11 orthogonal to the axis of the multipole device and parallel to
12 the axis of the TOF analyzer.

13 Atmospheric pressure ionization (API) includes a number of
14 methods. Typically, analyte ions are produced from liquid
15 solution at atmospheric pressure. One of the more widely used
16 methods, known as electrospray ionization (ESI), was first
17 suggested by Dole *et al.* (M. Dole, L.L. Mack, R.L. Hines, R.C.
18 Mobley, L.D. Ferguson, M.B. Alice, *J. Chem. Phys.* **49**, 2240,
19 1968). In the electrospray technique, analyte is dissolved in a
20 liquid solution and sprayed from a needle. The spray is induced
21 by the application of a potential difference between the needle

1 and a counter electrode. The spray results in the formation of
2 fine, charged droplets of solution containing analyte molecules.
3 In the gas phase, the solvent evaporates leaving behind charged,
4 gas phase, analyte ions. Very large ions can be formed in this
5 way. Ions as large as 1 MDa have been detected by ESI in
6 conjunction with mass spectrometry (ESMS).

7 ESMS was introduced by Yamashita and Fenn (M. Yamashita and
8 J.B. Fenn, *J. Phys. Chem.* **88**, 4671, 1984). To establish this
9 combination of ESI and MS, ions had to be formed at atmospheric
10 pressure, and then introduced into the vacuum system of a mass
11 analyzer via a differentially pumped interface. The combination
12 of ESI and MS afforded scientists the opportunity to mass analyze
13 a wide range of samples. ESMS is now widely used primarily in
14 the analysis of biomolecules (e.g. proteins) and complex organic
15 molecules.

16 In the intervening years a number of means and methods
17 useful to ESMS and API-MS have been developed. Specifically,
18 much work has focused on sprayers and ionization chambers. In
19 addition to the original electrospray technique, pneumatic
20 assisted electrospray, dual electrospray, and nano electrospray
21 are now also widely available. Pneumatic assisted electrospray

1 (A.P. Bruins, T.R. Covey, and J.D. Henion, Anal. Chem. 59, 2642,
2 1987) uses nebulizing gas flowing past the tip of the spray
3 needle to assist in the formation of droplets. The nebulization
4 gas assists in the formation of the spray and thereby makes the
5 operation of the ESI easier. Nano electrospray (M.S. Wilm, M.
6 Mann, *Int. J. Mass Spectrom. Ion Processes* 136, 167, 1994)
7 employs a much smaller diameter needle than the original
8 electrospray. As a result the flow rate of sample to the tip is
9 lower and the droplets in the spray are finer. However, the ion
10 signal provided by nano electrospray in conjunction with MS is
11 essentially the same as with the original electrospray. Nano
12 electrospray is therefore much more sensitive with respect to the
13 amount of material necessary to perform a given analysis.

14 An elevated pressure ion source always has an ion production
15 region (wherein ions are produced) and an ion transfer region
16 (wherein ions are transferred through differential pumping stages
17 and into the mass analyzer). The ion production region is at an
18 elevated pressure -- most often atmospheric pressure -- with
19 respect to the analyzer. The ion production region will often
20 include an ionization "chamber". In an ESI source, for example,
21 liquid samples are "sprayed" into the "chamber" to form ions.

1 Once the ions are produced, they must be transported to the
2 vacuum for mass analysis. Generally, mass spectrometers (MS)
3 operate in a vacuum between 10^{-4} and 10^{-10} torr depending on the
4 type of mass analyzer used. In order for the gas phase ions to
5 enter the mass analyzer, they must be separated from the
6 background gas carrying the ions and transported through the
7 single or multiple vacuum stages.

8 The use of multipole ion guides has been shown to be an
9 effective means of transporting ions through a vacuum system.
10 Publications by Olivers et al. (Anal. Chem, Vol. 59, p. 1230-
11 1232, 1987), Smith et al. (Anal. Chem. Vol. 60, p. 436-441, 1988)
12 and Douglas et al. U.S. Pat. No. 4,963,736 (Douglas) have
13 reported the use of AC-only quadrupole ion guides to transport
14 ions from an API source to a mass analyzer. Such multipole ion
15 guides may be configured as collision cells capable of being
16 operated in RF only mode with a variable DC offset potential
17 applied to all rods. Thomson et al., U.S. Patent Number
18 5,847,386 (Thomson) also describes a quadrupole ion guide. The
19 ion guide of Thomson is configured to create a DC axial field
20 along its axis to move ions axially through a collision cell,
21 *inter alia*, or to promote dissociation of ions (i.e., by

1 Collision Induced Dissociation (CID)).

2 Further, mass spectrometers similar to that of Whitehouse et
3 al. U.S. Patent No. 5,652,427, entitled "Multipole Ion Guide for
4 Mass Spectrometry", (Whitehouse) use multipole RF ion guides to
5 transfer ions from one pressure region to another in a
6 differentially pumped system. In the source of Whitehouse, ions
7 are produced by ESI or APCI at substantially atmospheric
8 pressure. These ions are transferred from atmospheric pressure
9 to a first differential pumping region by the gas flow through a
10 glass capillary. Ions are transferred from this first pumping
11 region to a second pumping region through a "skimmer" by an
12 electric field between these regions as well as gas flow. A
13 multipole in the second differentially pumped region accepts ions
14 of a selected mass/charge (m/z) ratio and guides them through a
15 restriction and into a third differentially pumped region. This
16 is accomplished by applying AC and DC voltages to the individual
17 poles.

18 A four vacuum stage ES/MS quadrupole mass spectrometer
19 according to Whitehouse, incorporating a multipole ion guide
20 beginning in one vacuum pumping stage and extending contiguously
21 into an adjacent pumping stage, is depicted in FIG. 1. As

1 discussed above, ions are formed from sample solution by an
2 electrospray process when a potential is applied between spray
3 needle 5 of sprayer 2 and sampling orifice 4. In other words,
4 sample solution enters the ionization chamber through spray
5 needle 5, at the end of which the solution is formed into a spray
6 of fine droplets (not shown). The spray is formed as a result of
7 an electrostatic field applied between spray needle 5 and
8 sampling orifice 7. The sampling orifice may be an aperture,
9 capillary, or other similar inlet leading into the differential
10 pumping regions of the mass spectrometer. According to the prior
11 art system shown in FIG. 1, capillary 16 is used to transport
12 ions from atmospheric pressure region 1, where the ions are
13 formed, to first pumping region 6. Lenses 10 and 14 are used to
14 guide the ions from the exit end of capillary 16 through third
15 pumping region 22 into a fourth pumping region 26 containing a
16 mass analyzer -- in this case a quadrupole mass analyzer.

17 Between lenses 10 and 30, an RF only hexapole ion guide 20
18 is used to guide ions through differential pumping stages 22 and
19 26 to exit 28 and into mass analysis region 32 through orifice
20 34. Ion guide 20 according to this prior art design is intended
21 to provide for the efficient transport of ions from one location

1 (i.e., the entrance of skimmer 14) to a second location (i.e.,
2 orifice 34). For the purpose of illustration, an electrospray
3 ion source is shown as the API source. This could alternatively
4 be an APCI or an ICP source.

5 Sample liquid is introduced through the electrospray needle
6 2 and is electrosprayed - either with or without pneumatic
7 assistance - into chamber 1 as it exits needle 2. The charged
8 droplets produced evaporate and desorb gas phase ions both in
9 chamber 1 and as they are swept into vacuum through the annulus
10 in capillary 16. A portion of the ions that enter first vacuum
11 stage 6 through the capillary exit are focused through skimmer 14
12 with the help of lens 10 and the potential set on the capillary
13 exit. Ions passing through skimmer 14 enter the multipole ion
14 guide 20 which begins in vacuum pumping stage 22 and extends
15 unbroken into vacuum stage 26. Ions falling within a certain m/z
16 range - determined in part by the frequency and amplitude of the
17 potentials applied to ion guide 20 - which enter multipole ion
18 guide 20 will be guided to multipole ion guide exit end 28 and
19 will be focused by exit lens 30 into the TOF analyzer region 32
20 through orifice 34 for subsequent analysis. Whitehouse also
21 discloses the use of collisional gas within ion guide 20 to cool

1 the ions to thermal velocities through collisional cooling.

2 In the scheme of Whitehouse, an RF only potential is applied
3 to ion guide 20. As a result, ion guide 20 is not "selective"
4 but rather transmits ions over a broad range of mass-to-charge
5 (m/z) ratios. Such a range as provided by prior art multipoles
6 is inadequate for certain applications, such as for Matrix
7 Assisted Laser Desorption/Ionization (MALDI), because the ions
8 produced may be well out of this m/z range. In other words, high
9 m/z ions such as are often produced by the MALDI ionization
10 method are often out of the range of transmission of conventional
11 multipole ion guides.

12 Thus, electric voltages usually applied to the conventional
13 ion guide are used to transmit ions from an entrance end to an
14 exit end. Analyte ions produced in the ion production region
15 pass through a capillary or other ion transfer device to move the
16 ions to a differentially pumped region and enter the ion guide at
17 the entrance end. Through collisions with gas in the ion guide,
18 the kinetic energy of the ions is reduced to thermal energies.
19 Simultaneously, the RF potential on the poles of the ion guide
20 forces ions to the axis of the ion guide. Then, ions migrate
21 through the ion guide toward its exit end, where the ions

1 typically either enter a second ion guide or enter the mass
2 analysis region.

3 Whitehouse also discloses use of two or more ion guides in
4 consecutive vacuum pumping stages to allow different DC and RF
5 values. However, losses in ion transmission efficiency may occur
6 in the region of static voltage lenses between ion guides. For
7 example, a commercially available API/MS instrument manufactured
8 by Hewlett Packard incorporates two skimmers and an ion guide.
9 The region between the skimmers is pumped by the drag stage of
10 the same turbopump which pumps the region containing the
11 multipole ion guide. That is, an additional pumping stage/region
12 is added without the addition of an extra turbo pump, and
13 therefore, improved pumping efficiency may be achieved. In this
14 dual skimmer design, there is no ion focusing device between
15 skimmers, therefore ion losses may occur as the gases are pumped
16 away. A second example is demonstrated by a commercially
17 available API/MS instrument manufactured by Finnigan which
18 applies an electrical static lens between capillary and skimmer
19 to focus the ion beam. Due to narrow mass range of the static
20 lens, the instrument may need to scan the voltage to optimize the
21 ion transmission.

1 In addition, the electrode rods of the prior art multipole
2 ion guides described above are positioned in parallel and are
3 equally spaced at a common radius from the centerline of the ion
4 guide. Thus, ions with a m/z ratio that fell within the ion
5 guide stability window established by the applied voltages would
6 have stable trajectories within the ion guide's internal volume
7 bounded by the parallel, evenly spaced rods. This is true for
8 quadrupoles, hexapoles, etc.

9 In other schemes a multipole might be used to guide ions of
10 a selected m/z through the transfer region. For example, Morris
11 et al., in H.R. Morris et al., High Sensitivity Collisionally
12 Activated Decomposition Tandem Mass Spectrometry on a Novel
13 Quadrupole/Orthogonal-Acceleration Time-of-Flight Mass
14 Spectrometer, *Rapid Commun. Mass Spectrom.* 10, 889 (1996), use a
15 series of multipoles in their design. One of these is a
16 quadrupole. The quadrupole can be run in a "wide bandpass" mode
17 or a "narrow bandpass" mode. In the wide bandpass mode, an RF-
18 only potential is applied to the quadrupole and ions of a
19 relatively broad range of m/z values are transmitted. In narrow
20 bandpass mode both RF and DC potentials are applied to the
21 quadrupole such that ions of only a narrow range of m/z values are

1 selected for transmission through the quadrupole. In subsequent
2 multipoles, the selected ions may be activated towards
3 dissociation. In this way the instrument of Morris et al. is
4 able to perform MS/MS experiments with a first mass analysis and
5 subsequent fragmentation occurring in what would otherwise be
6 simply a set of multipole ion guides.

7 Such a prior art ionization source according to Morris et
8 al. is shown in FIG. 2. This prior art source design is similar
9 to Whitehouse (as shown in FIG. 1), except for the multipole ion
10 guide arrangement. In the prior art source design according to
11 Morris et al., four RF multipoles 48, 50, 52 & 54 are used. The
12 first multipole encountered by the ions is hexapole 48. It is
13 used in a manner similar to the Whitehouse et al. to cool and
14 guide the ions. The second multipole encountered is quadrupole
15 50. Quadrupole 50 can be used in a wide bandpass mode to
16 transmit ions over a broad m/z range, or in a narrow bandpass
17 mode to transmit ions of a selected narrow m/z range. This leads
18 to the use of the mass spectrometer instrument in MS and MS/MS
19 modes. In MS mode, quadrupole 50 is operated as a wide bandpass
20 ion guide. Ions are simply transmitted by all four multipoles
21 48, 50, 52 & 54 to time-of-flight mass analyzer 62. The TOF mass

1 analyzer 62 is then used to produce a mass spectrum. In MS/MS
2 mode, quadrupole 50 is operated as a narrow bandpass ion guide to
3 select ions of interest.

4 Further, the ions encounter a third multipole -- hexapole 52
5 -- which is operated with a DC offset with respect to quadrupole
6 50 and contains a collision gas. This leads to collisions
7 between the ions of interest and the collision gas and can result
8 in the formation of fragment ions. Finally, the fragment ions
9 are guided by a fourth multipole -- hexapole 54 -- to TOF
10 analyzer 62 which is then used to produce a mass spectrum of
11 these fragment ions.

12 In the performance of tandem mass spectrometry experiments,
13 precursor ions are selected and fragmented, and the fragment ions
14 are analyzed to produce a fragment ion spectrum. In the prior
15 art, a variety of methods have been used to fragment precursor
16 ions. Among these are collision induced dissociation (CID) as
17 mentioned above, surface induced dissociation (SID), infrared
18 multiphoton dissociation (IRMPD), electron capture dissociation
19 (ECD), and many others. Each of these methods has its advantages
20 and disadvantages. For example, CID is a relatively simple
21 technique and can be applied in a variety of instrument

1 configurations (i.e. quadrupole, TOF, or FT-ICR analyzers). IRMPD
2 is somewhat more complex in that a laser is required, but has the
3 advantage that it produces no gas load on the vacuum system - as
4 is the case in CID - and can produce fragment species that are
5 inaccessible by CID. SID is also somewhat complex in that it is
6 necessary that a "collision surface" be prepared and placed in
7 the instrument. Also, SID is not readily adaptable to all types
8 of analyzers. However, SID does provides better control over the
9 fragmentation process and can lead to higher efficiency in the
10 production of useful fragment ions.

11 Quadrupole mass analyzers have been used in conjunction with
12 surface induced dissociation (SID). For example, Wysocki et al.
13 discloses such an arrangement (Chungang GU, Vincent J. Angelico,
14 Vicki H. Wysocki, Proceedings of the 46th ASMS conference on Mass
15 Spectrometry and Allied Topics, pg. 72(1998), Wysocki et al.,
16 Proceedings of the 47th ASMS Conference on Mass Spectrometry and
17 Allied Topics, pg. 2834, 2144, 1040, and 2299(1999), Ahok Dongre,
18 Vicki Wysocki, *Org. Mass Spectrom.* **29**, 700(1994), Thomas Kane,
19 Vincent Angelico, and Vicki Wysocki, *Langmuir* **13**, 6722(1997),
20 Chungang Gu, Vicki Wysocki, *J. AM. Chem. Soc.* **119**, 12010(1997),
21 Arpad Somogyi, Thomas Kane, Jian-Mei Ding, Vicki Wysocki, *J. AM.*

1 Chem. Soc. 115, 5275(1993), Thomas Kane, Vincent Angelico, Vicki
2 Wysocki, Anal. Chem. 66, 3733(1994), Thomas Kane, Vicki Wysocki,
3 Int. J. Mass. Spectrom. Ion Process 140, 177(1994), Vicki Wysocki
4 et al., Am. Soc. Mass. Spectrom. 3, 27(1992)). In such an
5 arrangement, as shown in FIG. 3, first quadrupole 81 comprising
6 rods 80 is used to select ions of a given m/z from a beam of
7 incoming ions 78. The selected ions are allowed to collide with
8 a SID "collision surface" 76 after passing through electrodes 82.
9 The instrument according to Wysocki can be operated without
10 fragmentation of the selected ions or with surface-induced
11 dissociation of the selected ions. In SID, the ions are
12 dissociated via energetic collisions with a prepared "collision
13 surface". This collision results in the fragmentation of the
14 selected ions into "fragment ions", and the fragment ions are
15 extracted (and focused by electrodes 84) into second quadrupole
16 85 comprising rods 86. Second quadrupole 85 is used to analyze
17 the these fragment ions.

18 In MS mode, or to produce simply a mass spectrum of the
19 incident ion beam, first quadrupole 81 is scanned over the mass
20 range of interest while second quadrupole 85 is operated in broad
21 bandpass mode (i.e., RF only). The potential between the source

1 (not shown) and collision surface 76 is held at zero volts. As a
2 result, ions exiting first quadrupole 81 do not strike collision
3 surface 76, but rather, these ions are deflected into second
4 quadrupole 85 which transmits them to a detector (not shown).

5 In SID MS/MS mode, first quadrupole 81 is used to select
6 ions of a given m/z out of the incident ion beam. These ions are
7 allowed to strike collision surface 76. The kinetic energy of
8 the ions when they strike surface 76 is determined largely by the
9 potential difference between the ion source (not shown) and
10 collision surface 76. Fragment ions resulting from the ion-
11 surface collision are extracted by an electrostatic field into
12 second quadrupole 85 where they are mass analyzed to produce a
13 fragment ion spectrum.

14 For example, FIGs. 4A-D depict the operation of the Q-SID-Q
15 instrument according to Wysocki without fragmentation due to SID
16 (FIGs. 4A-B) and with fragmentation due to SID (FIGs. 4C-D). In
17 MS mode, as shown in FIGs. 4A-B, no potential difference is
18 applied between source 90 and collision surface 96. In this
19 case, the ions are transmitted from source 90 through quadrupole
20 92, but do not strike collision surface 96 (as indicated by ion
21 path 94) and do not produce fragment ions. The ions then enter

1 quadrupole 98 for mass analysis. Therefore, because no fragment
2 ions are produced, the resulting mass spectrum 120 shown in FIG.
3 4B contains a single peak 100 -- that of the incident beam.

4 In SID MS/MS mode, as shown in FIGs. 4C-D, a potential
5 difference is applied between source 102 and collision surface
6 108. In this case, selected ions are transmitted from source 102
7 through ion guide 104, such that they strike collision surface
8 108 (at location 106 of the ion beam path). As a result of the
9 collision, ion fragments of the initial ion beam are formed (as
10 indicated at ion beam 110) and enter second quadrupole 112.
11 Second quadrupole 112 is used to mass analyze the fragment ion.
12 Once analyzed, these fragment ions then enter the detector (not
13 shown). The resulting sharp peaks 114 of the mass spectrum 116
14 shown in FIG. 4D depicts multiple m/z values of the fragment
15 ions.

16 The present invention provides means and method of using SID
17 in conjunction with any mass analyzer - in the preferred
18 embodiment, a TOF mass analyzer. More specifically, a first
19 multipole (preferably a quadrupole) is used to select precursor
20 ions, the ions are allowed to collide with a collision surface,
21 and the fragment ions thereby produced are collisionally cooled

1 in a second multipole and then mass analyzed in a mass analyzer
2 (preferably a TOF mass analyzer). Further, a method and
3 apparatus are described which use a plurality (preferably three)
4 of multipole devices, a collision surface (for SID), and/or a
5 collision gas (for CID) to produce fragment ions of a selected
6 m/z range (i.e., using a Q-SID-Q or Q-CID-Q arrangement) for
7 subsequent mass analysis (preferably in an orthogonal TOF mass
8 analyzer).

9
10 SUMMARY OF THE INVENTION

11 The purpose of the present invention is to provide a tandem
12 mass spectrometry instrument with improved performance
13 characteristics over prior art instruments. Particularly, the
14 preferred embodiment Q-SID-Q-TOF instrument according to the
15 present invention is capable of surface induced dissociation, and
16 collision induced dissociation. Thus, an instrument according to
17 the present invention can be used to take advantage of the
18 fragmentation characteristics of either of these methods. Also,
19 because a TOF mass analyzer is used in the preferred embodiment,
20 precursor and fragment ion spectra can be obtained rapidly - i.e.

1 on a time scale consistent with hyphenation of the instrument
2 with liquid chromatography.

3 Another object of the present invention is to provide a
4 means of adapting surface induced dissociation to any type of
5 mass analyzer. That is, SID is performed between two multipoles -
6 e.g. Q-SID-Q - followed by mass analysis in a mass analyzer of
7 choice - e.g. FT-ICR, quadrupole trap, etc.

8 Other objects, features, and characteristics of the present
9 invention, as well as the methods of operation and functions of
10 the related elements of the structure, and the combination of
11 parts and economies of manufacture, will become more apparent
12 upon consideration of the following detailed description with
13 reference to the accompanying drawings, all of which form a part
14 of this specification.

15

16 BRIEF DESCRIPTION OF THE DRAWINGS

17 A further understanding of the present invention can be
18 obtained by reference to a preferred embodiment set forth in the
19 illustrations of the accompanying drawings. Although the
20 illustrated embodiment is merely exemplary of systems for
21 carrying out the present invention, both the organization and

1 method of operation of the invention, in general, together with
2 further objectives and advantages thereof, may be more easily
3 understood by reference to the drawings and the following
4 description. The drawings are not intended to limit the scope of
5 this invention, which is set forth with particularity in the
6 claims as appended or as subsequently amended, but merely to
7 clarify and exemplify the invention.

8 For a more complete understanding of the present invention,
9 reference is now made to the following drawings in which:

10 FIG. 1 shows a conventional four vacuum stage ES/MS
11 quadrupole MS instrument according to Whitehouse;

12 FIG. 2 shows a prior art ionization source design according
13 to Morris;

14 FIG. 3 is a schematic representation of a prior art Q-SID-Q
15 instrument according to Wysocki;

16 FIGS. 4A and 4B depict the operation of the Q-SID-Q
17 instrument of FIG. 3 without fragmentation;

18 FIG. 4C and 4D depict the operation of the Q-SID-Q
19 instrument of FIG. 3 with fragmentation' (due to SID);

20 FIG. 5 is a diagrammatic representation of the preferred
21 embodiment of the Q-SID-Q-TOF mass spectrometer according to the

1 present invention;

2 FIG. 6 is a diagrammatic representation of an alternate
3 embodiment of the Q-SID-Q-TOF mass spectrometer according to the
4 present invention.

5

6 DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

7 As required, a detailed illustrative embodiment of the
8 present invention is disclosed herein. However, techniques,
9 systems and operating structures in accordance with the present
10 invention may be embodied in a wide variety of forms and modes,
11 some of which may be quite different from those in the disclosed
12 embodiment. Consequently, the specific structural and functional
13 details disclosed herein are merely representative, yet in that
14 regard, they are deemed to afford the best embodiment for
15 purposes of disclosure and to provide a basis for the claims
16 herein which define the scope of the present invention. The
17 following presents a detailed description of a preferred
18 embodiment (as well as some alternative embodiments) of the
19 present invention.

20 Referring first to FIG. 5, shown is diagrammatic
21 representation of the preferred embodiment of the Q-SID-Q-TOFMS

1 according to the present invention. Specifically, the preferred
2 embodiment of a quadrupole surface induced dissociation
3 quadrupole time-of-flight ("Q-SID-Q-TOF") mass spectrometer
4 according to the invention comprises ionization source 130, first
5 multipole 132 (preferably a hexapole), second multipole
6 (preferably a quadrupole) 140, collision surface 136 for surface
7 induced dissociation (SID), third multipole 138 (which optionally
8 acts as a collision cell for collision induced dissociation
9 (CID)), and mass analyzer 142 (preferably a time of flight mass
10 analyzer). Multipoles 132, 140, and 138 are preferably RF
11 multipoles similar to the RF multipole ion guides known in the
12 prior art.

13 As shown, first multipole 132 is disposed coaxial with and
14 downstream of ion source 130. Second multipole 140 is disposed
15 coaxial with and downstream of first multipole 132 and ion source
16 130, such that ions 134 are transported from ion source 130
17 through first multipole 132 into second multipole 140. Third
18 multipole 138 preferably contains a collision gas and is
19 positioned such that its axis is orthogonal to the axis of first
20 and second multipoles 132 & 140. Collision surface 136 is
21 disposed between second and third multipoles 140 & 138 with its

1 normal vector at an angle (preferably 45°) to the axis of
2 multipoles 140 & 138. Finally, TOF analyzer 142 is disposed
3 downstream of (and preferably orthogonal to) third multipole 138.

4 In the preferred embodiment, ion source 130 is an
5 electrospray ionization (ESI) source. Ions are produced at
6 atmospheric pressure and introduced into the vacuum system of the
7 instrument through an aperture or other opening in the vacuum
8 housing. Multipoles 132, 140, and 138 and analyzer 142 are
9 preferably disposed in different pumping regions of the vacuum
10 system. Multipole 132 in a first pumping region is maintained at
11 a pressure of 10^{-2} - 10^{-3} mbar. Multipole 140 and collision
12 surface 136, in a second pumping region, are maintained at a
13 pressure of about 10^{-5} mbar. Multipole 138, in a third pumping
14 region, is maintained at a pressure of 10^{-2} - 10^{-3} mbar. In the
15 preferred embodiment, the pressure in multipole 138 is achieved
16 by "leaking" a desired collision gas (e.g. N₂, Ar, He, etc.) into
17 the multipole. A dynamic equilibrium between the rate at which
18 gas is leaked into the multipole and the rate at which it is
19 pumped away and a desired pressure is thereby achieved. Analyzer
20 142 (preferably a TOF mass analyzer) is preferably maintained in
21 a fourth pumping region at a pressure of 10^{-7} mbar or less.

1 In the present invention, ions may be generated in any
2 conceivable ion source (i.e., an electrospray ionization source,
3 matrix assisted laser desorption/ionization, chemical ionization,
4 etc.). As these ions enter first multipole 132, they undergo
5 collisions with the gas therein. These collisions cause the ions
6 to lose kinetic energy and thereby to be cooled to near thermal
7 velocities. First multipole 132 guides the ions from the source
8 region to the entrance of second multipole 140.

9 In second multipole 140, ions of a desired mass-to-charge
10 ratio (m/z) range are selected. Ions falling outside the desired
11 m/z range are removed from the ion beam by the electric field of
12 multipole 140. Second multipole 140 is preferably a quadrupole.
13 To transmit ions over a broad range of m/z values, the DC
14 potential between the quadrupole rods is set to 0V and multipole
15 140 is thereby operated in "RF only" mode. Multipole 140 is
16 typically operated in RF only mode when generating a precursor
17 ion spectrum. To select ions of a narrow m/z range, both RF and
18 DC potentials are applied between the multipole rods as described
19 extensively in the prior art. Multipole 140 is typically operated
20 to select a narrow m/z range when generating a fragment ion
21 spectrum.

1 In the performance of SID experiments, selected ions (aka.
2 precursor ions) collide with collision surface 136 with a
3 predefined collision energy. The collision surface may consist of
4 a self assembled monolayer (preferably of straight chain
5 hydrocarbons with fluorinated end groups). The preparation and
6 use of collision surfaces for SID is described extensively in the
7 literature. The predefined collision energy is given by the
8 difference in the DC levels between multipole 132 and collision
9 surface 136 (e.g. 20V). As detailed in prior art literature, a
10 number of reactions can take place as a result of the ion-surface
11 collision. Among these are neutralization, abstraction, and
12 fragmentation. Products species (ideally fragment ions) are
13 focused into multipole 138 by the potential difference between
14 surface 136 and multipole 138 and by other ion optical elements
15 (not shown) known in the prior art. Through collisions with gas
16 in multipole 138, the fragment and remaining precursor ions are
17 cooled to thermal energies. Multipole 138 guides the cooled ions
18 to analyzer 142. Mass analyzer 142 (preferably a TOF analyzer) is
19 then used to generate a mass spectrum of the ions - aka. a
20 fragment ion spectrum.

21 Alternatively, in "MS only" analyses and in the performance

1 of CID experiments, the DC potential difference between multipole
2 132 and collision surface 136 is maintained at 0V. Selected ions
3 then do not collide with collision surface 136, but rather
4 continue on into multipole 138. In "MS only" analyses, second
5 multipole 140 is typically operated in RF only mode to transmit
6 ions over a broad m/z range. The kinetic energy of ion entering
7 multipole 138 is low - e.g. 5 eV. Through collisions with gas in
8 multipole 138, the ions are again cooled to thermal energies.
9 Multipole 138 guides the cooled ions to analyzer 142. Mass
10 analyzer 142 (preferably a TOF analyzer) is used to generate a
11 mass spectrum of the ions.

12 In the performance of CID experiments, the kinetic energy of
13 ions entering multipole 138 is high - e.g. 100 eV. This kinetic
14 energy is set by the DC potential difference between multipoles
15 132 and 138. Through initial collisions with gas (e.g. N₂, Ar,
16 etc.) in multipole 138, ions are activated towards fragmentation.
17 Fragment ions resulting from CID, as well as precursor ions, are
18 then "cooled" to thermal energies via subsequent collisions with
19 the gas in multipole 138. Multipole 138 also guides the ions
20 into mass analyzer 142. Mass analyzer 142 (preferably a TOF
21 analyzer) subsequently analyzes the fragment and precursor ions

1 and produces a fragment ion spectrum.

2 Furthermore, alternate embodiments of the present invention
3 are not limited to three multipoles. Multipoles consisting of
4 any number of rods may be used instead of quadrupoles. Also,
5 ions selected by multipole 140 may be used as primary ions in the
6 production of secondary ions from surface 136. In this way, the
7 instrument may be used for SIMS analysis of a solid sample. That
8 is, samples are deposited on a holder to form surface 136. Ions
9 selected by multipole 140 collide with the sample inducing the
10 sputtering of sample ions from sample material composing surface
11 136. These ions are focused into multipole 138, cooled by
12 collisions with the gas in multipole 138 and guided into analyzer
13 142. Mass analyzer 142 (preferably a TOF analyzer) then produces
14 a mass spectrum from these ions - i.e. a secondary ion mass
15 spectrum (SIMS).

16 Additionally, a laser may be used to perform MALDI
17 experiments from surface 136. In this embodiment, MALDI samples
18 are deposited on a holder to form surface 136. A laser is used
19 to produce ions from the MALDI samples, and the MALDI ions are
20 extracted into the multipole 138. These ions are focused into
21 multipole 138, cooled by collisions with the gas in multipole 138

1 and guided into analyzer 142. Mass analyzer 142 (preferably a TOF
2 analyzer) then produces a mass spectrum from these ions - i.e. a
3 secondary ion mass spectrum (SIMS)..

4 Additionally, an IR laser may be used to irradiate ions
5 while they are in one of multipoles 132, 140, or 138 in order to
6 perform "in source" IRMPD in the manner described by Steven
7 Hoffstadler.

8 Finally, other types of mass analyzers may be used instead
9 of TOF (e.g., FTICR, quadrupole ion traps, etc.).

10 Turning next to FIG. 6, shown is an alternate embodiment of
11 the Q-SID-Q-TOFMS according to the present invention.
12 Specifically, depicted is a diagrammatic representation of a
13 quadrupole surface induced dissociation quadrupole time-of-flight
14 ("Q-SID-Q-TOF") mass spectrometer according to the invention
15 comprising, similar to FIG. 5, ionization source 130, first
16 multipole 132 (preferably a hexapole), second multipole
17 (preferably a quadrupole) 140, collision surface 136 for surface
18 induced dissociation (SID), third multipole 138 (which optionally
19 acts as a collision cell for collision induced dissociation
20 (CID)), and mass analyzer 142 (preferably a time of flight mass
21 analyzer).

1 As shown in FIG. 6, the Q-SID-Q-TOF according to the
2 invention may be used with a coaxial multiple reflection TOF mass
3 analyzer 142, such as that described in US patent number
4 6,107,625, which is herein incorporated by reference. Such a
5 mass analyzer 142 comprises an "orthogonal interface" with
6 respect to the Q-SID-Q-TOF (i.e., ion guide 138 is positioned
7 orthogonal to the axis of the TOF analyzer 142), a drift region
8 152, reflectron 154, detectors 144 and/or 156, accelerator 146,
9 and optionally, multideflector 148, all oriented coaxially with
10 one another. The mass analyzer accepts ions from the external
11 ion source 130, via ion guides 132, 140 and 138, and accelerates
12 them toward reflectron 154. If reflectron 154 is energized, the
13 ions are reflected back toward detector 144. In this case the m/z
14 of the ions are determined by the time required for the ions to
15 travel from accelerator 146 to reflectron 154, to detector 144.
16 If reflectron 154 is deenergized, ions travel directly from
17 accelerator 146 to detector 156. Similarly, the m/z of the ions
18 is determined by the time required to travel from accelerator 146
19 to detector 156. Although the TOF analyzer depicted in figure 6
20 is a "coaxial" analyzer design, it should be recognized that any
21 other prior art TOF analyzer design might be substituted for the

1 depicted analyzer.

2 While the present invention has been described with
3 reference to one or more preferred embodiments, such embodiments
4 are merely exemplary and are not intended to be limiting or
5 represent an exhaustive enumeration of all aspects of the
6 invention. The scope of the invention, therefore, shall be
7 defined solely by the following claims. Further, it will be
8 apparent to those of skill in the art that numerous changes may
9 be made in such details without departing from the spirit and the
10 principles of the invention. It should be appreciated that the
11 present invention is capable of being embodied in other forms
12 without departing from its essential characteristics.